CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-085

STATISTICAL REVIEW(S)

NOV - 9 1999

Statistical Review and Evaluation

NDA: 21-085
Drug Name: Avelox®(moxifloxacin hydrochloride) 400-mg tablets
Applicant: Bayer Corporation
Indications: (1) Sinusitis;
(2) Acute exacerbation of chronic bronchitis (AECB);
(3) Community-acquired pneumonia (CAP);

[redacted]

Documents Reviewed: CANDA, dated December 10, 1998. Electronic data resubmitted on April 17, 1999
Medical Officer: Eric Mann, M.D., HFD-520, Andrea Meyerhoff, M.D., John Powers, M.D., Eileen Navarro, M.D., and Leonard Sacks, M.D., from HFD-590

[redacted]

1. Introduction

NDA 21-085 for Avelox®(moxifloxacin hydrochloride) 400-mg tablets was submitted as a New Drug Application by Bayer Corporation with four indications. These four indications are:

(1) **Acute sinusitis** caused by *Streptococcus pneumoniae* (including penicillin susceptible, intermediate and resistant strains), *Haemophilus influenzae,* or *Moraxella catarrhalis.*

(2) **Acute exacerbation of chronic bronchitis** caused by *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Staphylococcus aureus,* or *Moraxella catarrhalis.*

(3) **Community-acquired pneumonia** caused by *Streptococcus pneumoniae* (including penicillin susceptible, intermediate and resistant strains), *Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae, Klebsiella pneumoniae, Staphylococcus aureus,* or *Moraxella catarrhalis.*

The primary source data for this application are derived from 38 clinical pharmacology studies, 18 studies in the claimed indications (sinusitis, 6 studies; AECB, 4 studies; CAP, 5 studies,

The development program was carried out globally. The clinical pharmacology studies involved 691 subjects, 634 of whom were treated with moxifloxacin. Across all studies in patients with infectious conditions (i.e., the claimed indications and the other studies), a total of 4996 patients were enrolled in either the 200 mg or 400 mg moxifloxacin treatment groups. Of these 4996 patients, 4926 took at least one dose and were considered evaluable for safety, 556 of whom received ~~200 mg~~ per day and 4370 of whom received 400 mg per day. A total of 3448 patients were enrolled in one of the control treatment groups, and 3415 of them were evaluable for safety. A list of the studies in patients with infectious conditions (ie, the claimed indications and the other studies) is provided in Table 1.

Table 1 - Studies of moxifloxacin in patients with infectious conditions

Indication	Controlled Studies US	Controlled Studies non-US	Uncontrolled Studies US	Uncontrolled Studies Non-US
Sinusitis	100107[a,b] D96-024[a]	0161[a] 0116[a] 0109	D96-023[a]	
Acute exacerbation of chronic bronchitis (AECB)	D96-027[a] D96-022[a]	0124[a] 0106		
Community-acquired pneumonia (CAP)	D96-026[a]	0119[a] 0140[a] 0112	D96-025[a]	

[a] Pivotal study

[b] Database for Study 100107 was not available as of 10 September 1998 data lock to Bayer Corporation for the Integrated Summary of Safety. But, the results of this trial will be included in this review.

The review of this NDA will be organized by indications. This review will also focus on the controlled US studies. The original design of each study will be summarized in the review first, followed by the Applicant's results and the reviewer's comments and his own analysis, if any. Some safety issues are also addressed in this review. Finally, the overall assessment will be presented.

2. Acute Sinusitis

Table 2 identifies the studies of moxifloxacin in Sinusitis. For each study this table provides key design features. A total of six studies were conducted with moxifloxacin in acute, bacterial, maxillary sinusitis.

Four Phase III trials (100107, 0161, 0116, D96-024) were designed to be adequate and well-controlled trials to demonstrate efficacy and safety of 7 or 10 days of moxifloxacin treatment for acute sinusitis. Together with D96-023, an uncontrolled trial, they were intended to support labeled claims for this indication. Studies 100107, 0161, 0116, D96-024 were randomized, multicenter, parallel-group, active-controlled, and double blind. In particular, studies 100107 and D96-024 were conducted in North America (i.e., the United States and Canada). Study 100107 was to compare moxifloxacin 400-mg QD 10 days with Cefuroxime Axetil 250-mg BID 10 days while Study D96-024 was to compare moxifloxacin 400-mg QD 7 days with Cefuroxime Axetil 250-mg BID 10 days. As the 7-day moxifloxacin group showed a lower cure rate than its comparator in study D96-024, the applicant agreed to pursue the 10-day moxifloxacin treatment only. For this reason, studies 100107 and 0161 are important to support the Applicant's suggested labeling.

Table 2. Studies of Sinusitis

Protocol #/ Country	Trial Design	Treatment/Dose	Duration of Treatment	# Patients /group (Total)
#100107 US	Controlled, double -blind, parallel group, randomized Phase III	Cefuroxime Axetil 250 mg BID x 10 days Moxifloxacin 400 mg QD x 10 days	10 days 10 days	275 267 (542)
#0161 SF, F, D, GR, IL, LT, GB	Controlled, double blind, parallel group, randomized Phase III	Moxifloxacin 400 mg QD x 10 days Cefuroxime Axetil 250 mg BID x 10 days	10 days 10 days	246 251 (497)
#0116 D, E, F, GR, IL, S, SF	Controlled, double blind, parallel group, randomized Phase III	Moxifloxacin 400 mg QD x 7 days Cefuroxime Axetil 250 mg BID x 10 days	7 days 10 days	244 254 (498)
D96-023 US	Uncontrolled, open label, -, non-randomized Phase III	Moxifloxacin 400 mg QD x 7 days	7 days	372 (372)
D96-024 US, CA	Controlled, double blind, parallel group, randomized Phase III	Moxifloxacin 400 mg QD x 7 days Cefuroxime Axetil 250 mg BID x 10 days	7 days 10 days	238 233 (471)
#0109 EST, LT	Controlled, open label, parallel group, randomized Phase IIA	Moxifloxacin 200 mg QD x 7-14 days Moxifloxacin 400 mg QD x 7-14 days Clarithromycin 500 mg BID x 7-14 days	7-14 days 7-14 days 7-14 days	26 27 27 (86)

2.1 Study 100107 and Its Parallel Study 0161

2.1.1 Design of Studies

The design of Study 100107 and Study 0161 was to compare a 10-day treatment of moxifloxacin therapy with a 10-day treatment of cefuroxime axetil therapy. Study assessments were performed at 4 study visits. The screening visit (48 hours or less before the first dose of study drug), the during-therapy visit (Day 3-5 in Study 100107 and Day 7-9 in Study 0161), the end-of-therapy visit (7-21 days after the last dose of study drug in Study 100107 and 4-19 days after the last dose in Study 0161), and the follow-up visit (21 to 37 days after the last dose of study drug in Study 100107 and 20 to 30 days after the last dose in Study 0161). The primary efficacy evaluation proposed by the Applicant was at the end of therapy. The FDA's time window for the test of cure as determined by the reviewing medical officer was at 1-month follow-up (i.e., at the follow-up visit).

Efficacy was evaluated on the basis of signs and symptoms (none, mild, moderate, or severe) and clinical response (eg, resolution, failure, indeterminate). Safety was evaluated on the basis of adverse events and laboratory tests.

For a course of therapy to be judged valid for evaluating the efficacy of drug therapy in the per protocol (PP) analysis, the following criteria were specified in the protocols to be met: acute sinusitis must have been confirmed at pre-treatment by the presence of signs and symptoms of infection; pretherapy x-ray consistent with acute bacterial maxillary sinusitis; available pre- and post-therapy sinus x-rays; treatment duration had to be at least 48 hours (for clinical failure), or at least 5 days (for clinical success); no other systemic antimicrobial agent could have been administered during the study period (up through post-therapy evaluation) unless the patient was a treatment failure; adequate compliance with 80% or more of oral study medication administered must have been documented; there could be no protocol violation influencing treatment efficacy; and no essential data (ie, affecting the primary efficacy variable) could be missing or indeterminate.

The Applicant considered the PP analysis the primary analysis and did not even perform an ITT analysis. The protocol specified that the equivalence of efficacy would be established if the lower bound of the 95% confidence interval around difference of clinical response rates 14-17 days post-treatment was greater than –10%.

2.1.2 Applicant's Main Analysis

In Study 100107, there were 457 patients valid for clinical efficacy, 223 in the moxifloxacin 400 mg QD x 10-day group and 234 in the cefuroxime axetil 250 mg BID x 10-day group. Overall, 16% of the patients enrolled were not valid for the primary efficacy analysis. The most common reasons for invalidity were "insufficient duration of therapy" (5%), "violation of inclusion/exclusion criteria" (4%),"violation of time schedule" (3%), and "essential data missing or invalid" (3%). "Essential data missing or invalid" (3%) was the code used for patients who had an evaluation that was done outside of the end of therapy window, day +7 to +21, or for whom an assessment of their clinical status could not be made due to an "indeterminate" assessment by the site. A total of 5 patients (0.9%) were excluded from safety analysis because they were lost to follow-up and it could not be documented whether or not they had received any study medication. The treatment groups were similar with respect to demographic and baseline variables, with the exception of severity of infection (% moderate = 74% in patients who received moxifloxacin and 83% in patients who received cefuroxime axetil, p = 0.033) and number of patients with left sinus infections in the last 6 months (6% in patients who received moxifloxacin and 2% in patients who received cefuroxime axetil, p = 0.050). There were also more severe infections in the moxifloxacin group than in the cefuroxime axetil group (21% versus 15%). Mean duration of infection, and the proportion with individual signs and symptoms of sinusitis, were similar for the treatment groups.

In Study 0161, there were 439 patients valid for clinical efficacy, 217 in the moxifloxacin 400 mg QD x 10-day group and 222 in the cefuroxime axetil 250 mg BID x 10-day group. A subgroup of 158 patients were valid for microbiological efficacy evaluation, 86 in the moxifloxacin group and 72 in the cefuroxime axetil group. Overall, 12% of the patients enrolled were not valid for the primary efficacy analysis. The most common reasons for invalidity were "violation of time schedule" (7%), "use of prohibited concomitant medication" (5%), "violation of inclusion/exclusion criteria" (4%), "essential data missing or invalid" (4%), and "insufficient duration of therapy" (3%). Two patients were lost to follow-up, one of whom did not receive any study medication.

Short Statistical Comments: The compliance of these two studies is very common, although not ideal, in this type of clinical trial. Clinical outcomes of each patient at the last visit will be given by this reviewer in the next section.

In study 100107, success rates for the primary efficacy variable in the clinically evaluable population were 89.7% for the moxifloxacin group and 89.3% for the cefuroxime axetil group. The 95% confidence interval for the treatment group difference in response rates was (-5.1%, 6.2%). The response was evaluated at the end of therapy visit, i.e., 7 to 21 days post treatment.

In Study 0161, the primary efficacy parameters was "resolution" as clinical response at TOC. Resolution rates of the clinically evaluable population were 93.5 % in the moxifloxacin group as compared to 94.6 % in the cefuroxime group. The 95 % confidence interval calculated for the difference of clinical success rates at the end of therapy visit, (moxifloxacin minus cefuroxime-axetil), was (-5.5 %, 3.4 %).

Short Statistical Comments: Dr. Mann, the reviewing Medical Officer, found that some patients who did not have purulent nasal drainage and malar tenderness/pain were included in the evaluable population of the Applicant's Per Protocol analysis. The MO's analysis will exclude those patients and require drugs to show improvement of both symptoms to be called a cure. The FDA's primary analysis will be the evaluation at the follow-up visit. See analysis in the next section.

2.1.3 Reviewer's Analysis and Comments

ITT analysis

The information of clinical outcomes of patients at their last visit and their use of alternative antibiotics therapy is useful to assess the compliance and efficacy of compared treatments in the controlled studies. As the Applicant did not adequately present this information in their submission, the reviewer will present it here. Two methods are used in the ITT populations.

Method I (Loss to follow-up as failure): The following rules are followed: (1) cure and improvement is combined as a success of the treatment; (2) failure and indeterminate are combined and treated as a failure in the analysis; (3) patients who used alternative antibiotic are treated as failures in the ITT analysis whatever the actual outcomes are; (4) patients who were lost to follow-up before the primary post therapy visit are treated as failures.

Method II (Carry last observation forward): The following rules are followed: (1) cure and improvement is combined as a success of the treatment; (2) failure and indeterminate are combined and treated as ~~a failure~~ in the analysis; (3) patients who used alternative antibiotic are treated as failures in the ITT analysis whatever the actual outcomes are. (4) last observed outcome is treated as the ultimate outcome and carried forward.

Neither of the two methods will recover the information lost due to the lack of follow-up or contamination of response by using other antibiotic agents. However, they let us view the merits of these clinical trials and drug effects from different angles. These two methods will be used repeatedly through out the review.

Table 3. Study 100107: Summary of last observation of clinical outcomes (cure/improvement/failure/indeterminate)

Last visit at	400mg moxiflo	250mg cefuroxime-axetil
During therapy	0/2/0/0	0/6/0/1
Early post therapy	13/0/4/2	7/0/4/2
Late post therapy	207/0/5/1	216/1/6/1
Other antibiotic	17/0/6/1	24/0/3/2

In study 100107, lost to follow-up (i.e., last visit occurs prior to late post therapy), alternative antibiotic use and indeterminate outcome are major factors which cause uncertainty of the ITT analysis. 46/258 (17.8%) and 50/273 (18.3%) of patients in 400mg moxifloxacin and 250mg cefuroxime-axetil, respectively, do not have a purely treatment-directed clinical outcome at the late post therapy visit due to any of these three factors.

Using Method I, treating lost to follow-up as failures, the success rates are 80.29% (207/258) and 79.1% (216/273), respectively, for 400mg moxifloxacin and 250mg cefuroxime-axetil. The 2-sided 95% confidence interval for the difference, 400 mg moxifloxacin vs 250 mg cefuroxime-axetil is (-6.1%, 8.3%).

Using Method II, carrying last observation forward, the success rates are 86.0% (222/258) and 83.9% (229/273), respectively, for 400mg moxifloxacin and 250mg cefuroxime-axetil. The 2-sided 95% confidence interval for the difference, 400 mg moxifloxacin vs 250 mg cefuroxime-axetil is (-4.3%, 8.6%).

Table 4. Study 0161: Summary of last observation of clinical outcomes (cure/improvement/failure/indeterminate)

Last visit at	400mg moxifloxacin	250mg cefuroxime-axetil
Pre therapy	0/0/0/4	0/0/0/2
During therapy	1/0/0/0	0/1/0/0
Early post therapy	7/0/1/0	4/0/1/0
Late post therapy	201/0/10/5	213/0/14/1
Other antibiotic	15/0/2/0	13/0/1/1

In study 0161, loss to follow-up (i.e., last visit occurs prior to late post therapy), alternative antibiotic use and indeterminate outcome are major factors which cause uncertainty of the ITT analysis. 35/246 (14.2%) and 24/251 (9.5%) of patients in 400mg moxifloxacin and 250mg cefuroxime-axetil, respectively, do not have a purely treatment-directed clinical outcome at the late post therapy visit due to any of these three factors.

Using Method I, the success rates are 81.7% (201/246) and 84.9% (213/251), respectively for 400mg moxifloxacin and 250mg cefuroxime-axetil . The 2-sided 95% confidence interval for the difference, 400mg moxifloxacin vs 250mg cefuroxime-axetil, is (-10.1%, 3.8%).

Using Method II, the successful rate is 85.0% (209/246), 86.5% (217/251), respectively for 400mg moxifloxacin and 250mg cefuroxime-axetil . The 2-sided 95% confidence interval for the differences, 400mg moxifloxacin vs 250mg cefuroxime-axetil is (-8.1%, 5.1%).

Per Protocol analysis:

As we pointed out earlier, the Medical Officer required that patients should have a symptom of either purulent nasal drainage or malar tenderness/pain to be qualified for the PP analysis. He also required that a clinical success should show improvement in both symptoms (i.e., for both symptoms, if originally scored as a 1, an improvement must be scored 0 at TOC; if originally scored greater than 1, an improvement must be scored 1 or 0 at TOC). The Medical Officer's results of 100107 and 0161 are presented here.

In study 100107, 445 patients are in the new PP population. The cure rates of 400mg moxifloxacin and 250mg cefuroxime-axetil are 77.4%(168/217) and 81.6%(186/228), respectively. The 95% CI for the difference is (-12.1%,3.8%).

In study 0161, 424 patients are in the new PP population. The cure rates of 400mg moxifloxacin and 250mg cefuroxime-axetil are 87.1%(183/210) and 88.8%(190/214), respectively. The 95% CI for the difference is (-8.3%,5.0%).

Conclusions: All ITT and PP analyses except the PP analysis of study 100107 showed that a 10-day regimen of 400 mg moxifloxacin QD is equivalent to the cefuroxime-axetil regimen, given that a delta of 10% is used for defining equivalence. The lower bound of confidence interval for the difference of response rates in the PP analysis of study 100107 is –12.1%, which is considered close to –10% limit.

2.2 Study D96-24 and Study 0116

Study D96-024 and Study 0116 were designed to compare the safety and clinical efficacy of moxifloxacin 400 mg administered orally (PO) once a day for 7 days and of cefuroxime axetil 250 mg PO twice a day (BID) for 10 days in the treatment of adults with clinically documented acute bacterial maxillary sinusitis. Other features except treatment duration are very similar to the design of 100107.

2.2.1 Applicant's Main Analysis

In Study D96-024, of the 471 patients enrolled (238 in the moxifloxacin group and 233 in the cefuroxime axetil group), 448 completed the study. Among them, 222 (93%) in the moxifloxacin group and 226 (97%) in the cefuroxime axetil group. Adverse events were the main reason for discontinuation of treatment in both treatment groups (11 in the moxifloxacin group and 5 in the Cefuroxime group).

In Study 0116, of the 498 enrolled patients, 493 patients (99.0%) received at least one dose of study medication and hence were eligible for the intent-to-treat population and safety analysis (242 patients in the moxifloxacin arm and 251 patients in the cefuroxime-axetil arm). Among the five patients who were excluded from the ITT/safety analysis, four patients withdrew their consent (and did not receive any study medication) and one patient was lost to follow-up (never receiving any study medication).

A total of 384 (81.5%) patients in Study D96-024 and 436 (87.6%) patients in Study 0116 were valid for the PP analysis of efficacy. In Study D96-0124, 191 in the moxifloxacin group and 193 in the cefuroxime group were evaluable; in Study 0116, 211 patients in the moxifloxacin arm and 225 patients in the cefuroxime-axetil arm were evaluable.

The overall clinical response rates of moxifloxacin and Cefuroxime Axetil are 81% (154/191) and 91% (176/193) in Study D96-024, 89.7% (175/195) and 83.5% (177/212) in Study 0116, respectively. The 95% confidence interval for the difference in success rates (moxifloxacin minus cefuroxime axetil) for the overall response is (-17.1%, -3.8%) for Study D96-024 and (-0.8%, 13.3%) for Study 0116. The results of these two studies are contradictory.

Short Statistical Comments: The baseline characteristics and the profile of patients who remain in the efficacy analysis in both studies are similar for the two treatment groups. The non-evaluability rates are moderate and the main reasons for non-evaluability are missing data, violation of time schedule, violation of inclusion/exclusion criteria, and insufficient doses. The 7-day treatment of moxifloxacin is less efficacious than the 10-day treatment of cefuroxime axetil in Study D96-024. But in a similarly designed study 0116 conducted in the European countries, patients treated with 7-day moxifloxacin had higher observed response rate than patients treated with 10-day cefuroxime axetil. The ITT analysis based on the applicant's assessment of each patient and PP analysis based on the Medical Officer's method as described in the previous section are given in the next section.

2.2.2 Reviewer's Analysis and Comments

ITT Analysis:

Similar to the previous section, the information of clinical outcomes of patients at their last visit and their use of alternative antibiotic therapy is summarized in the following table. Two methods of analysis (Carrying last observation forward and treating missing data as failures) are applied to the ITT populations.

Table 5. Study D96-024: Summary of last observation of clinical outcomes (cure/improvement/failure/indeterminate)

Last visit at	400mg moxiflo	250mg cefuroxime-axetil
During therapy	0/1/0/0	0/3/0/0
End of therapy	5/0/5/4	4/0/0/1
Late post therapy	177/1/7/3	196/0/3/2
Other antibiotic	23/0/9/1	17/0/6/1

In study D96-024, loss to follow-up (i.e., last visit occurs prior to late post therapy), alternative antibiotic use and indeterminate outcome are major factors which cause uncertainty of the ITT analysis. 51/236 (21.6%) and 34/233 (14.6%) of patients in 400mg moxifloxacin and 250mg cefuroxime-axetil, respectively, do not have a purely treatment-directed clinical outcome at the late post therapy visit due to any of these three factors.

Using the method of treating lost to follow up and use of alternate antibiotics as failures (Method I), the success rates are 75.4% (178/236), 84.1% (196/233), respectively for 400mg moxifloxacin and

250mg cefuroxime-axetil . The 2-sided 95% confidence interval for the difference, 400mg moxifloxacin vs 250mg cefuroxime-axetil, is (-16.3%, -1.0%).

Using the method of carrying last observation forward and treating use of alternate antibiotics as failures (Method II), the success rates are 78.0% (184/236) and 87.1% (203/233), respectively for 400mg moxifloxacin and 250mg cefuroxime-axetil . The 2-sided 95% confidence interval for the difference, 400mg moxifloxacin vs 250mg cefuroxime-axetil, is (-16.4%, -1.9%).

Table 6. Study 0116: Summary of last observation of clinical outcomes (cure/improvement/failure/indeterminate)

Last visit at	400mg moxiflo x 7 days	250mg cefuroxime-axetil
During therapy	1/2/0/1	0/0/0/0
End of therapy	6/0/2/0	6/0/1/1
Late post therapy	201/0/13/10	200/0/12/14
Other antibiotic	2/0/0/3	12/0/1/3

In study 0116, loss to follow-up (i.e., last visit occurs prior to late post therapy), alternative antibiotic use and indeterminate outcome are major factors which cause uncertainty of the ITT analysis. 27/241 (11.2%) and 38/250 (15.2%) of patients in 400mg moxifloxacin and 250mg cefuroxime-axetil, respectively, do not have a purely treatment-directed clinical outcome at the late post therapy visit due to any of these three factors.

Using Method I, the success rates are 83.4% (201/241) and 80.0% (200/250), respectively for 400mg moxifloxacin and 250mg cefuroxime-axetil . The 2-sided 95% confidence interval for the difference, 400mg moxifloxacin vs 250mg cefuroxime-axetil is (-3.8%, 10.6%).

Using Method II, the success rates are 87.1% (210/241), 82.4% (206/250), respectively for 400mg moxifloxacin and 250mg cefuroxime-axetil. The 2-sided 95% confidence interval for the difference, 400mg moxifloxacin vs 250mg cefuroxime-axetil, is (-2.0%, 11.5%).

Per Protocol Analysis

The same method as is described in the section 2.1.3, PP analysis using the Medical Officer's criteria is conducted and presented below.

In Study D96-024, 371 patients are in the new PP population. The cure rates of 400mg moxifloxacin and 250mg cefuroxime-axetil are 75.1%(139/185) and 88.7%(165/186), respectively. The 95% CI for the difference is (-21.8%,-5.3%).

In study 0116, 425 patients are in the new PP population. The cure rates of 400mg moxifloxacin x 7 days and 250mg cefuroxime-axetil are 87.0%(180/207) and 81.2%(177/218), respectively. The 95% CI for the difference is (-1.6%, 13.2%).

Conclusions: The 7-day regimen of 400mg moxifloxacin should not be approved based on the fact that this regimen failed to demonstrate clinical equivalence to the approved treatment in Study D96-024.

2.3 Statistical Conclusions

Basically, studies 100107 and 0161 showed that a 10 day regimen of moxafloxicin is as efficacious as cefuroxime in the treatment of sinusitis. The lower bounds of the 95% CI for the difference of moxifloxacin minus cefuroxime in success rates are close to –10% in study 100107 and greater than –10% in study 0161, respectively. The 7-day treatment with moxifloxacin yields a significantly lower success rate than the 10-day treatment of cefuroxime for sinusitis in Study D96-024. As a result, it will be much more reliable to treat sinusitis with 10 days of moxifloxacin rather than with 7 days of moxifloxacin.

3. Acute Exacerbation of Chronic Bronchitis (AECB)

Table 7 identifies the studies of moxifloxacin in AECB. For each study this table provides key design features. A total of three studies were conducted with moxifloxacin groups in adults with acute exacerbation of chronic bronchitis. Two of the three studies, D96-027 and 0124 included a moxifloxacin dosing regimen consistent with the proposed labeling (400 mg for 5 days). Study D96-027 is a randomized comparative study conducted in the US while study 0124 is a comparative study carried out in Europe. Therefore, D96-027 is considered the pivotal study of this indication. Statistical adjustment for the comparison of multiple dose of test drug with the control will be considered. Study D96-022 compares one 400 mg x 10-day regimen of moxifloxacin and one 200 mg x 10-day regimen of moxifloxacin with a 500 mg x 10-day regimen of Cefuroxime. Therefore, it will be considered as a supporting study.

Table 7- Summary of Studies That are Basis for Efficacy Claims (Patients Enrolled) in AECB

Study #	Country	moxifloxacin Regimen	# of Patients	Comparator	# of Patients
D96-022	United States	200 mg x10 days 400 mg x 10 days	223 225	Cefuroxime 500 mg x10 days	234
D96-027	United States	400 mg x 10 days 400 mg x 5 days	307 316	Clarithromycin 500 mg BID x 7days	313
0124	Europe*	400 mg x 5 days	374	Clarithromycin 500 mg BID x 7 days	371
Total Patients		moxifloxacin	1220	Comparators	918

* Europe - Austria, France, Germany, Greece, Spain, Switzerland, United Kingdom

3.1 Design of Study D96-027 and Study 0124

Despite some difference in the key design features of these studies, the inclusion/exclusion criteria, patient management, primary evaluating variables and visits are very similar in these three trials. Patients were evaluated five times with clinical signs and symptoms collected at each visit. The primary efficacy parameter was the clinical response at the Test-of-Cure visit (i.e., the visit held +7 to +17 days after the last dose of study medication) in the clinically evaluable population.

Secondary efficacy parameters consisted of the bacteriological response in the clinically and microbiologically evaluable population and at the pathogen level, eradication rates for causative organisms isolated at baseline.

For a course to be judged valid for evaluating the efficacy of drug therapy in the PP analysis, the following criteria must have been met: the patients must have been ≥18 years of age with underlying chronic bronchitis as defined by the daily production of sputum most days for at least 3 consecutive months for more than 2 consecutive years; acute signs and symptoms of the infection must have been present; no other anti-microbial agent could have been administered concomitantly with the study drug; the study drug was given for a minimum of 48 hours (for failures) or a minimum of 5 days if the result was a success; compliance with dosing was ≥80%; a pre-therapy sputum specimen for culture was obtained; there were no protocol violations influencing treatment efficacy; the random code was not broken; and there were no missing or indeterminate data affecting the primary efficacy variable. For a microbiologically valid course, at least one causative organism must have been identified at pre-therapy culture and an appropriate therapy bacteriological evaluation must have been carried out.

For the actual analysis, the POST 1 (+7 to +17 day) follow-up time point was still used as the primary time point. For the primary variable, end of therapy failures were carried forward and included as overall failures. The window for the POST II visit was expanded from +21 to +28 to +18 to +31 days. At the February 1998 pre-NDA meeting, the FDA statistical reviewer requested that as an additional statistical method, a normal approximation to the binomial distribution, with a continuity correction, be used for the confidence interval for the treatment group differences, therefore, this method was used. The protocol specified that the equivalence of efficacy would be established if the lower bound of 95% confidence interval for the difference of clinical response rates is greater than –15%.

3.2 Study D96-027

3.2.1 Applicant's Main Analyses

Patient demographics and disposition information is summarized in the following table. The number of patients who discontinued treatment in the comparator group is greater than the other two groups treated with moxifloxacin. Those who had insufficient therapeutic effect were considered failures in analyses.

Among total patients enrolled, 66/316 (20.9%) patients in the 5 days moxifloxacin 400mg QD group, 51/307 (16.6%) patients in the 10 days moxifloxacin 400mg QD group and 62/313 (19.8%) patients in the 10 days clarithromycin 500mg BID group were non-evaluable for PP analysis. The major reasons for non-evaluability were missing data, violation of inclusion/exclusion criteria, insufficient treatment duration or lost to follow up.

Table 8 - Patient Demographics and Disposition - Intent-to-Treat Population

	Moxifloxacin 400 mg QD x 5 days	Moxifloxacin 400 mg QD x 10 days	Clarithromycin 500 mg BID x 10 days
Number enrolled	316	307	313
Age range (Mean age)	19-88 (57)	18-88 (56)	18-88 (56)
% Male/female	54/45	55/45	51/49
% Black/white/other	22/76/2	23/75/2	27/71/2
Number of discontinuations	25	24	51
Adverse events	13 (4%)	13 (4%)	21 (7%)
Insufficient therapeutic effect	3 (<1%)	1 (<1%)	21 (7%)
Lost to follow-up	8 (3%)	8 (3%)	2 (<1%)
Protocol violation	1 (<1%)	2 (<1%)	7 (2%)

Analysis of the primary efficacy parameter in this trial (overall clinical response +7 to +17 days after the last dose of drug) showed that a response rate of 89% for the moxifloxacin x 5-day group, 91% for the moxifloxacin x 10-day group, and 89% for the clarithromycin group. The 95% Confidence intervals for the difference in the response rates are presented in table 9.

Table 9 Clinical Response at Test-of-Cure* (Study D96-027)

	Moxifloxacin 400 mg x 5 days	Moxifloxacin 400 mg x 10 days	Clarithromycin 500 mg BID x 10 days
Test-of-Cure (+7 to +17 Days Post)	222/250 (89%)	234/256 (91%)	224/251 (89%)

95% Confidence Interval: (moxifloxacin x 10-days - Clarithromycin) = (-2.7%, 7.2%)
95% Confidence Interval: (moxifloxacin x 5-days - Clarithromycin) = (-6.1%, 4.2%)
95% Confidence Interval: (moxifloxacin x 5-days - moxifloxacin x 10-days) = (-7.4%, 2.7%)

Short Statistical Comments: Multiple regimens of moxifloxacin (400 mg x 10 days, 400 mg x 5 days) were compared with a single regimen of Clarithromycin. A multiplicity adjustment, such as the Bonferroni Adjustment, is needed to cope with this problem. As a result, 97.5% confidence intervals are presented by this reviewer in the next section.

Eradication rates at follow-up were 89% and 91% for moxifloxacin x 5 days and moxifloxacin x 10 days, respectively, the same as the overall clinical response success rates for those groups. The eradication rate at follow-up (day +7 to +17) for the clarithromycin group was 85%, slightly lower than the 89% overall clinical response success rate.

Table 10 – Bacteriological Response Rates (Study D96-027)

	Moxifloxacin 400 mg x 5 days	Moxifloxacin 400 mg x 10 days	Clarithromycin 500 mg BID x 10 days
Post Therapy (day +7 to +17)	127/143 (89%)*	135/148 (91%)	110/129 (85%)

* # eradicated/total # patients with isolates(%). 95% Confidence Interval: (moxifloxacin x 10 days - Clarithromycin) = (0.3%, 14.5%) (moxifloxacin x 5 days - Clarithromycin) = (-3.7%, 10.5%)

Short Statistical Comments: Bacteriological response rates and eradication rates of target organisms will be scrutinized by the Medical Officer. Please refer to his review for this issue.

3.2.2 Reviewer's Analysis and Comments

The information of clinical outcomes of patients at their last visit and their use of alternative antibiotics is summarized in the following table. Two methods of analysis (treating missing data as failures and carrying last observation forward) are applied to the ITT populations.

Table 12. Study D96-027: Summary of last observation of clinical outcomes (cure/improvement/failure/indeterminate)

Last visit at	400mg Moxiflo x 10 days	400mg moxiflo x 5 days	500mg Clarithromycin
During therapy	0/4/0/0	0/5/0/0	0/3/0/0
End of therapy	2/6/1/4	4/6/4/3	7/2/8/5
Early post therapy	5/0/0/0	5/0/1/0	7/0/0/1
Late post therapy	233/0/12/0	229/0/12/2	219/0/11/3
Other antibiotic	26/0/7/3	37/0/2/3	31/0/9/4

Loss to follow-up (i.e., last visit occurs prior to late post therapy), alternative antibiotic use and indeterminate outcome are major factors which cause uncertainty of the ITT analysis. 58/303 (19.1%), 72/313 (23.0%) and 72/302 (23.8%) of patients in 400mg x 10 days moxifloxacin, 400mg x 5 days moxifloxacin and 500mg cefuroxime-axetil, respectively, do not have a purely treatment-directed clinical outcome at the late post therapy visit due to any of these three factors.

ITT Analysis: Using the method of treating loss to follow-up as failures (Method I), the success rates are 76.9% (233/303), 73.2% (229/313), 72.3% (219/303), respectively for 400mg moxifloxacin x 10 days, 400mg moxifloxacin x 5 days and 500mg cefuroxime-axetil. The 2-sided 97.5% confidence intervals for the differences, 400mg moxifloxacin x 10 days vs 500mg Cefuro-Axetil and 400mg moxifloxacin x 5 days vs 500mg cefuroxime-axetil respectively, are (-3.6%, 12.9%) and (-7.5%, 9.3%).

Using the method of carrying last observation forward (Method II), the success rates are 82.5% (250/303), 79.6% (249/313) and 78.5% (238/303), respectively for 400mg moxifloxacin x 10 days, 400mg moxifloxacin x 5 days and 500mg cefuroxime-axetil. The 2-sided 97.5% confidence intervals for the differences, 400mg moxifloxacin x 10 days vs 500mg Cefuro-Axetil and 400mg

moxifloxacin x 5 days vs 500mg cefuroxime-axetil respectively, are (-3.6%, 11.5%) and (-6.7%, 8.7%).

PP Analysis: The Medical Officer validated the compliance and outcome of each patient enrolled in this trial and decided to accept the Applicant's per protocol analysis. Because multiple doses of moxifloxacin were used in this study, statistical adjustment such as Bonferroni Adjustment is necessary to avoid the Type I error inflation. The 97.5% confidence intervals for the difference of cure rates, i.e., the confidence intervals based on Bonferroni Adjustment, are (-4.1%, 8.4%) for 400mg moxifloxacin x 10 days vs 500mg Cefuro-Axetil and (-7.1%, 6.2%) for 400mg moxifloxacin x 5 days vs 500mg cefuroxime-axetil, respectively.

3.3 Study 0124

3.3.1 Applicant's Main Analysis

Study 0124 was intended to enroll at least 632 patients. Seven-hundred and fifty patients were enrolled (376 to moxifloxacin, 373 to clarithromycin, 1 not randomised). Five patients were excluded from the ITT/safety analysis (3 patients received no study medication, 1 patient had no information on study drug treatment documented and 1 patient was not randomised). The remaining 745 patients were assigned to the analysis populations (intention-to-treat, valid for efficacy per-protocol, microbiologically valid) as follows:

	Intent–to-treat	**Per Protocol**	**Microb. valid**
moxifloxacin	374	322	115
Clarithromycin	371	327	114
Total	745	649	229

There were 52 withdrawals in the study, 32 in the moxifloxacin group (23 due to adverse events) and 19 in the clarithromycin group (14 due to adverse events).

The PP population (clinical response at day 14 analysis) included 649 patients. One-hundred and one patients were invalidated, most often because of insufficient duration of therapy, essential data missing and/or violation of visit time schedule. Analysis of the primary efficacy parameter (clinical response at day 14, i.e. 7 days after the end of study drug treatment, in the PP population) confirmed the statistical hypothesis that 400 mg moxifloxacin administered once daily for 5 days was not less effective than 500 mg clarithromycin administered twice daily for 7 days. The results for this and the secondary clinical efficacy parameters (PP population) are summarised below:-

	moxifloxacin		**Clarithromycin**	
Primary efficacy parameter:				
Clinical response day 14				
Total	322	(100 %)	327	(100 %)
Clinical cure	287	(89.1 %)	289	(88.4 %)
Clinical failure	35	(10.9 %)	38	(11.6 %)

The calculated 95 % confidence interval for the difference of the clinical success rates at day 14 (moxifloxacin minus clarithromycin) was (-3.9 %, 5.8 %).

Secondary efficacy parameters:

Clinical response at follow-up (combined day 14 and 1-month follow-up analysis)*

Total	331	(100 %)	338	(100 %)
Clinical cure	271	(81.9 %)	270	(79.9 %)
Clinical failure	60	(18.1 %)	68	(20.1 %)

* failures from day 14 carried forward to 1 month follow-up visit.

Short Statistical Comments: The Medical Officer validated the compliance and outcome of each patient enrolled in this trial and decided to accept the Applicant's evaluation for patients at each visit. The confidence interval was validated by the statistical reviewer who believes it reflected the equivalent treatment effect of the two drugs in the study. Furthermore, ITT analysis and the information of each patient's last clinical outcome were provided in the next section to further depict the similarity of the two drugs.

3.3.2 Reviewer's Analysis and Comments

In Table 13, loss to follow-up (i.e., last visit occurs prior to late post therapy), alternative antibiotic use and indeterminate outcome are major factors which cause uncertainty of the ITT analysis. 69/371 (18.6%) of patients in 400mg x 5 days moxifloxacin group and 71/367 (19.3%) of patients in 500mg clarithromycin 7 days, respectively, do not have a purely treatment-directed clinical outcome at the late post therapy visit due to any of these three factors.

Table 13. Study 0124: Summary of last observation of clinical outcomes (cure/improvement/failure/indeterminate)

Last visit at	400mg moxiflo x 5 days	500mg Clarithromycin 7 days
During therapy	0/0/0/0	0/0/0/0
End of therapy	0/0/0/1	1/0/0/2
Day 14 post therapy	2/0/0/0	4/0/0/0
Late post therapy	287/0/15/14	281/0/15/7
Other antibiotic	42/4/4/3	39/5/9/4

Using the method of treating loss to follow-up as failures (Method I), the success rates are 77.4% (287/371) and 76.6% (281/367), respectively for 400mg moxifloxacin x 5 days and 500mg . Clarithromycin 7 days The 2-sided 95% confidence interval for the difference, 400mg moxifloxacin x 5 days vs 500mg Clarithromycin 7 days, is (-5.6%, 7.1%).

Using the method of carrying last observation forward (Method II), the success rates are 77.9% (289/371) and 77.9% (286/367), respectively for 400mg moxifloxacin x 5 days and 500mg . Clarithromycin 7 days The 2-sided 95% confidence interval for the difference, 400mg moxifloxacin x 5 days vs 500mg Clarithromycin 7 days, is (-6.3%, 6.2%).

3.4 Conclusions

Both Study D96-027 and Study 0124 confirm that the regimens of 400mg x 5 days moxifloxacin and 500mg clarithromycin 7~10 days have equivalent efficacy rates in the treatment of AECB.

4. Community-acquired pneumonia (CAP)

Four of the studies (D96-026, D96-025, 0119, 0140) were Phase III trials and were considered to be adequate and well-controlled trials intended to support labeled claims for this indication. Table 15 identifies the studies that are the basis for efficacy claims for the community-acquired pneumonia indication. This reviewer will focus on the controlled US studies with a regimen of 400 mg moxifloxacin daily for 10 days as proposed in the labeling.

Table 15 – Summary of Studies That are Basis for Efficacy Claims (Patients Enrolled) in CAP

Study #	Country	Moxifloxacin Regimen	# of Patients	Comparator	# of Patients
D96-025	United States	400 mg x 10 days	254	-	-
D96-026	United States	400 mg x 10 days	237	Clarithromycin 500 mg BID x 10 days	237
0140	Europe/ROW[a]	400 mg x 10 days	203	Amoxicillin 1000 mg TID x 10 days	208
0119	Europe/ROW[b]	200 mg x 10 days	229	Clarithromycin 500 mg BID x 10 days	222
		400 mg x 10 days	224		
Total patients		Moxifloxacin	1147	Comparator	667

[a]Europe: Estonia, France, Lithuania, Portugal, Spain, United Kingdom; ROW (regions of the world): Argentina, Brazil, Chile, Croatia, Czech Republic, Hong-Kong, Mexico, Russia, Slovenia, South Africa, Turkey, Ukraine, Uruguay

[b]Europe: Austria, Germany,Greece, Italy, Norway, Sweden, Switzerland United Kingdom; ROW: Australia, Hong-Kong, Indonesia, Israel, New Zealand, Philippines, South Africa, Taiwan

4.1 Design of Studies

Despite those differences in key features of the four clinical trials shown in above table, many other aspects of design of these trials are similar. During the 10-day treatment period, there was to be an office visit (Day 3-5) evaluation of safety and efficacy. If the patient did not show improvement within 3-5 days (therapeutic failure), study drug therapy was to be discontinued and other appropriate therapy instituted. After completion of treatment, there were to be end of therapy (at 2 to 4 days after last dose of study drug, Days +2 to +4) and follow-up (at 21 to 28 days after last dose of study drug, Days +21 to +28) evaluations of safety and efficacy, the latter being considered the Test-of-Cure visit. Clinical and bacteriological responses to antimicrobial treatment were to be

evaluated based on signs and symptoms of CAP and sputum culture at the end of therapy and follow-up visits. Clinical response at TOC was considered the primary efficacy variable. In those patients determined to be therapeutic failures, clinical response to alternative antimicrobial therapy was to be assessed at 2 to 4 days after completion of alternative therapy. A delta of 10% in study D96-026 and a delta of 15% in study 0140 and study 0119 were specified in the protocol as the lower bound limit for the equivalence.

4.2 Study D96-026

4.2.1 Applicant's Main Analysis

Number of subjects/subject disposition is presented in the following table. No significant imbalance of gender, age and cause of discontinuation to treatment was found in this study. More clarithromycin patients discontinued study due to adverse events.

Table 16 – Patient Demographics and Disposition – Intent-to-Treat Population (Study D96-026)

	Moxifloxacin 400 mg QD x 10 days	Clarithromycin 500 mg BID x 10 days
Number enrolled	237	237
Age range (Mean age)	18-88 (48)	18-92 (49)
% Male/female	46/54	51/49
% Black/white/other	18/76/6	12/84/4
Number of discontinuations	13	19
Adverse events	6	12
Insufficient therapeutic effect	3	3
Lost to follow-up	1	4
Protocol violation	3	0

Among the total patients enrolled, 43/237 (18.1%) patients in the moxifloxacin group and 49/237 (20.7%) patients in the clarithromycin group were non-valid for PP analysis. The major reasons for non-evaluability are violation of inclusion/exclusion criteria, lost to follow-up, insufficient treatment duration, violation of visit schedule and use prohibited medications. In the PP analysis, moxifloxacin was statistically equivalent to clarithromycin in terms of overall clinical response at the Test-of-Cure visit in the clinically evaluable population (Table 17).

Table 17 – Overall Clinical Response At Test-of-Cure Visit in the Clinically Evaluable Population (Study D96-026)

	moxifloxacin 400 mg QD x 10 days	Clarithromycin 500 mg BID x 10 days
Test-of-Cure (+14 to +35 days Post)	184/194 (94.8%)	178/188 (94.7%)

95% Mantel-Haenszel Confidence Interval: (moxifloxacin -clarithromycin) = (-3.7%, 5.3%), Yates' continuity correction = (-4.8%, 5.2%)

Moxifloxacin was also statistically equivalent to clarithromycin for the overall clinical response in the clinically and microbiologically valid population (Table 18). In this population, the most common organisms were the atypical organisms *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* (as determined through cultures and/or serology testing). Among organisms obtained exclusively from sputum cultures, *Streptococcus pneumoniae* and *Haemophilus influenzae* were the most common organisms.

Table 18. Overall Clinical Response At Test-of-Cure Visit in Clinically and Microbiologically Evaluable Population (Study D96-026)

	moxifloxacin 400 mg QD x 10 days	Clarithromycin 500 mg BID x 10 days
Test-of-Cure	107/110 (97%)	102/104 (98%)

95% confidence interval: (moxifloxacin-clarithromycin) Yates' continuity correction = (-5.8%, 4.2%)

Short Statistical Comments: The Medical Officer validated the compliance and outcome of each patient enrolled in this trial and decided to accept the Applicant's evaluation for patients at each visit. This statistical reviewer confirmed these efficacy rates in per protocol population. In addition, the statistical reviewer tabulated the last clinical outcome of each patient in the following table to assess the quality of clinical trial and efficacy of the drugs.

4.2.2 Reviewer's Analysis

Table 19. Study D96-026: Summary of last observation of clinical outcomes (cure/improvement/failure/indeterminate)

Last visit at	400mg moxiflo x 10 days	500mg Clarithromycin 10 days
During therapy	0/2/0/0	0/1/0/0
End of therapy	7/2/2/3	8/6/0/5
Post therapy	196/0/2/0	191/0/1/0
Other antibiotic	15/0/3/5	17/0/3/3/

Loss to follow-up (i.e., last visit occurs prior to late post therapy), alternative antibiotic use and indeterminate outcome are major factors which cause uncertainty of the ITT analysis. 39/237 (16.5%) and 43/235 (18.3%) of patients in 400mg x 10 days moxifloxacin, and 500mg clarithromycin 10 days, respectively, do not have a purely treatment directed clinical outcome at the late post therapy visit due to any of these three factors.

Using Method I (treating loss to follow-up as failures), the success rates are 82.7% (196/237) and 81.3% (191/235), respectively for 400mg moxifloxacin x 10 days and 500mg Clarithromycin 10 days. The 2-sided 95% confidence interval for the difference, 400mg moxifloxacin x 5 days vs 500mg, is (-5.9%, 8.8%).

Using Method II (carrying last observation forward), the success rates are 87.3% (207/237) and 87.7% (206/235), respectively for 400mg moxifloxacin x 10 days and 500mg Clarithromycin 10 days. The 2-sided 95% confidence interval for the difference, 400mg moxifloxacin x 5 days vs 500mg, is (-6.7%, 6.1%).

4.3 Study 0140

4.3.1 Applicant's Analysis

Study 0140 is an European study which was to compare the clinical response of moxifloxacin 400 mg PO once daily for 10 days versus amoxicillin 1 gm PO TID for 10 days in the treatment of patients with suspected community-acquired pneumococcal pneumonia. Similarly as to Study D96-026, the Medical Officer accepted the Applicant's evaluation and asked the Statistical reviewer to confirm their analysis. The following results were validated by the Statistical reviewer.

Table 20 - Patient Demographics and Disposition - Intent-to-Treat Population (Study 0140)

	Moxifloxacin 400 mg QD x 10 days	Amoxicillin 1,000 mg TID x 10 days
Number enrolled	203	208
Age range (Mean age)	18-88 (51)	18-89 (50)
% Male/female	60/40	62/38
% Black/white/other	13/57/30	6/55/39
Number of discontinuations	14	18
Adverse events	6	5
Insufficient therapeutic effect	5	10
Lost to follow-up	0	3
Protocol violation	3	0

Forty-three moxifloxacin patients and thirty amoxicillin patients are not eveluable for the PP analysis at TOC. The major reasons include violation of inclusion/exclusion criteria, use prohibited medicines, lost to follow-up and insufficient treatment duration. In the PP analysis, moxifloxacin was statistically equivalent to amoxicillin in terms of overall clinical response at the Test-of-Cure Visit in the clinically evaluable population.

Table 21- Overall Clinical Response At Test-of-Cure Visit in Clinically Evaluable Population (Study 0140)

	moxifloxacin 400 mg QD x 10 days	Amoxicillin 1,000 mg TID x 10 days
Test-of-Cure[1] (+15 to +40 days Post)	143/160 (89%)	159/178 (89%)

[1] Clinically evaluable patients who were a resolution or indeterminate at end of therapy and did not have a valid Test-of-Cure visit were excluded from this analysis.
95% Mantel-Haenszel Confidence Interval adjusted for center: (moxifloxacin - Clarithromycin) = (-6.6%, 6.7%)
95% Confidence Interval: Yates' Continuity Correction = (-7.1%, 7.2%)

The bacteriological response at the Test-of-Cure visit for moxifloxacin was similar to that for amoxicillin.

Table 22 The Bacteriological Response At Test-of-Cure Visit in Clinically and Microbiologically Evaluable Patients (Study 0140)

	moxifloxacin 400 mg QD x 10 days	Amoxicillin 1,000 mg TID x 10 days
Eradication + Presumed Eradication*	49/58 (84%)	53/65 (82%)

95% Confidence Interval: (moxifloxacin - Clarithromycin), Yates' Continuity Correction (-11.9%, 17.8%)

4.3.2 Reviewer's Analysis

ITT analysis and the information of each patient's last clinical outcome are provided in the following table to further assess the equivalence of the two drugs.

Table 23. Summary of last observation of clinical outcomes (cure/improvement/failure/indeterminate)

Last visit at	400mg moxiflo x 10 days	1000mg Amoxicillin tid
During therapy	0/1/0/0	0/4/2/1
Early post therapy	7/0/0/2	3/0/0/1
Late post therapy	154/0/0/0	164/0/0/8
Other antibiotic	24/0/1/1	22/0/0/1

Loss to follow-up (i.e., last visit occurs prior to late post therapy), alternative antibiotic use and indeterminate outcome are major factors which cause uncertainty of the ITT analysis. 36/190 (18.9%) and 42/206 (20.4%) of patients in 400mg x 10 days moxifloxacin and 1000mg Amoxicillin, respectively, do not have a purely treatment-directed clinical outcome at the late post therapy visit due to any of these three factors.

Using Method I, the success rates are 81.1% (154/190) and 79.6% (164/206), respectively for 400mg moxifloxacin x 10 days and 1000mg Amoxicillin. The 2-sided 95% confidence interval for the difference, 400mg moxifloxacin x 5 days vs 500mg, is (-6.9%, 9.8%).

Using Method II, the success rates are 85.3% (162/190) and 83.0% (171/206), respectively for 400mg moxifloxacin x 10 days and 1000mg Amoxicillin. The 2-sided 95% confidence interval for the difference, 400mg moxifloxacin x 5 days vs 500mg, is (-5.4%, 10.0%).

4.4 European Study 0119

Study 0119 was to compare the clinical response at end of therapy (i.e. 3 to 5 days after the end of study treatment) for moxifloxacin 200 mg or 400 mg PO once daily for 10 days versus clarithromycin 500 mg PO twice daily for 10 days in the treatment of CAP. Secondary objectives were to compare the clinical response of the three regimens at the follow-up time point (i.e. 21 to 28 days after the end of study treatment), to compare the bacteriological response of the three regimens at the end of therapy and follow-up time points, and to compare the clinical and bacteriological response at the during therapy time point (i.e. day 3 to 5 after the start of therapy). Other design features were very similar with the US studies.

FDA reviewers considered the late follow-up visit to be the TOC visit.

4.4.1 Applicant's Analysis

Number of subjects/subject disposition is presented below.

Table 24- Patient Demographics and Disposition - Intent-to-Treat (Study 0119)

	moxifloxacin 200 mg x 10 days	Moxifloxacin 400 mg x 10 days	Clarithromycin 500 mg x 10 day
Number enrolled	229	224	222
Age range (Mean age)	17-88 (48)	18-93 (48)	18-92 (48)
% Male/female	62/38	61/39	62/38
% Black/white/other	28/59/13	29/59/12	27/59/14
Number of discontinuations	43	44	33
Adverse events	11	13	15
Insufficient therapeutic effect	11	7	4
Lost to follow-up	20	23	13
Protocol violation	1	1	1

Two hundred and eight patients (68 in the moxifloxacin 200mg 10 days group, 72 in the moxifloxacin 400mg 10 days group and 69 in the clarithromycin 500mg 10 days group) are not evaluable. The major reasons for non-evaluability are missing data, non-compliance with the study drug, violation of inclusion/exclusion criteria, use of prohibited medication, etc. For the efficacy parameter of overall clinical response at the Test-of-Cure Visit, both moxifloxacin regimens were

equivalent to the control regimen and each other as they were measured by the 95% confidence intervals.

Table 25 - Overall Clinical Response At Test-Of-Cure Visit In Clinically Evaluable Population (Study 0119)

	moxifloxacin 200 mg QD x 10 days	Moxifloxacin 400 mg QD x 10 days	Clarithromycin 500 mg BID x 10 days
Test-of-Cure[1] (+21 to +44 days Post)	146/161 (90.7%)	141/152 (92.8%)	141/153 (92.2%)

1 95% Mantel-Haenzel Confidence Intervals adjusted for center: (moxifloxacin 400 mg - Clarithromycin) = (-8.6%, 4.5%), (moxifloxacin 200 mg - Clarithromycin) = (-7.5%, 5.2%) and (moxifloxacin 200 mg - moxifloxacin 400 mg) = (-8.2%, 4.1%).
95% Confidence Intervals, Yates' continuity correction: (-6.0%, 7.2%), (-8.3%, 5.4%) and (-8.8%, 4.7%) for the 3 comparisons, respectively.

In Study 0119, less than 30% of patients were clinically and microbiologically evaluable in each treatment group. For this population at the Test-of-Cure Visit, the overall clinical response is reported in Table 26. The response rates were similar for the three regimens.

Table 26 – Overall Clinical Response At Test-Of-Cure Visit In Clinically And Microbiologically Evaluable Population[1] (Study 0119)

	moxifloxacin 200 mg QD x 10 days	Moxifloxacin 400 mg QD x 10 days	Clarithromycin 500 mg BID x 10 days
Test-of-Cure[1] (+21 to +44 days Post)	29/33 (88%)	29/34 (85%)	31/38 (82%)

1 Clinically and microbiologically evaluable patients who were a resolution or indeterminate at end of therapy and did not have a valid Test-of-Cure visit are excluded.
95% Confidence Intervals, Yates' continuity correction: (-16.2%, 23.6%), (-13.1%, 25.7%) and (-16.7%, 21.9%) for the 3 comparisons, respectively.

Statistical Comments: When Bonferroni Adjustment is used for comparison of two moxifloxacin regimens to the clarithromycin group, the 97.5% confidence interval for the difference is (-9.2%, 6.2%) for 10-day of 200 mg moxifloxacin minus 10-day of 500 mg clarithromycin, and (-6.8%, 8.0%) for the 10-day of 400 mg moxifloxacin minus 500 mg clarithromycin. Because non-evaluability rates are high in the treatment groups, the results of ITT analysis should be taken more seriously in our assessment of the efficacy of moxifloxacin.

4.4.2 Reviewer's Analysis

ITT analysis and the information of each patient's last clinical outcome are provided in the following table to further illustrate the equivalence of the two drugs.

Table 27. Summary of last observation of clinical outcomes (cure/improvement/failure/indeterminate)

Last visit at	200mg Moxiflo	400mg moxiflo	500mg Clarithromy
Before therapy	0/0/0/2	0/0/0/0	0/0/0/4
During therapy	0/12/4/1	0/7/1/2	0/9/4/0
End of therapy	12/0/0/4	19/0/0/2	12/0/0/1
Late post therapy	145/0/2/9	135/0/5/5/	147/0/1/8
Other antibiotic	0/38/0/3	0/34/1/4	0/33/1/4

Loss to follow-up (i.e., last visit occurs prior to late post therapy), alternative antibiotic use and indeterminate outcome are major factors which cause uncertainty of the ITT analysis. 69/216 (31.9%), 75/215 (34.9%) and 76/224 (33.9%) of patients in 200mg moxifloxacin, 400mg moxifloxacin and 500mg Clarithromycin, respectively, do not have a purely treatment directed clinical outcome at the late post therapy visit due to any of these three factors.

Using the method of treating loss to follow-up as failures (Method I), the success rates are 67.1% (145/216), 62.8% (135/215) and 65.6% (146/224), respectively for 200mg moxifloxacin, 400mg moxifloxacin and 500mg clarithromycin. The 2-sided 97.5% confidence intervals for the differences, 200mg moxifloxacin vs 500mg clarithromycin and 400mg moxifloxacin vs 500mg clarithromycinl respectively, are (-8.6%, 12.5%) and (-13.1%, 8.3%).

Using the method of carrying last observation forward (Method II), the success rates are 78.2% (169/216), 74.9% (161/215) and 75.0% (168/224), respectively for 200mg moxifloxacin, 400mg moxifloxacin and 500mg clarithromycin. The 2-sided 97.5% confidence intervals for the differences, 200mg moxifloxacin vs 500mg clarithromycin and 400mg moxifloxacin vs 500mg clarithromycin respectively, are (-6.2%, 12.7%) and (-9.8%, 9.6%).

4.5 Conclusions

All three comparative studies, D96-026, 0140 and 0119 confirm that the regimen of 400mg x 10 days moxifloxacin is equivalent to the regimens of 500mg clarithromycin 10 days or 1000 mg Amoxicillin 10 days in the treatment of CAP.

10 pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.

7. Overall Conclusions

This NDA demonstrated the efficacy equivalence of moxifloxacin in its proposed regimens to the compared drugs in the treatment of sinusitis, acute exacerbation of chronic bronchitis (AECB), community-acquired pneumonia (CAP) [redacted] The profile of adverse events between moxifloxacin and its compared treatments are similar. No alarming liver toxicity was found in the Phase III trials. There is a positive association of QTc prolongation and moxifloxacin concentration. The rate of QTc prolongation is about 5 msec increase per each 1000 mg/L of moxifloxacin in serum. Paired ECG changes from baseline were also found to be statistically significantly different between moxifloxacin and the controls in two out of nine Phase III trials. Large fluctuations of QTc were also found in placebo patients in Phase I/II trials. This observation makes it more difficult to interpret the outliers of QTc in the data submitted. Given the mixed signals of QTc data, the balance of benefit and risk of moxifloxacin for the pursued indications will need to be weighed by the Medical reviewers.

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